FORM PTO-1390 REV. 2/01 · U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
05823.0193

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
09/786276

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/KR00/01170	October 18, 2000	October 18, 1999

TITLE OF INVENTION: PREPARING METHOD OF CHIRAL ESTER

APPLICANT(S) FOR DO/EO/US: Jai Wook PARK; Mahn-Joo KIM; Jeong Hwan KOH; Hyun Min JUNG

Applicant(s) herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31)..
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed with the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)).
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☒ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A Substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154 (d)(4).
19. ☐ A second copy of the English language translation of the international application 35 U.S.C. 154 (d)(4).
20. ☒ Other items or information:
   a. ☐ Copy of cover page of International Publication No. WO
   b. ☐ Copy of Notification of Missing Requirements.
   c. ☒ Copy of PCT Request.

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/786276	INTERNATIONAL APPLICATION NO. PCT/KR00/01170	ATTORNEY'S DOCKET NUMBER 05823.0193

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33 (1)-(4) **$100.00**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$1000.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total Claims	9	- 20 =		x $18.00	$	
Independent Claims	1	-3 =		x $80.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+$270.00	$	
TOTAL OF THE ABOVE CALCULATIONS =					$1000.00	
☐ Applicant claims small entity status. Sec 37 CFR 1.27. The fees indicated above are reduced by ½.					$	
SUBTOTAL =					$1000.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest priority date (37 CFR 1.492(f)).					$	
TOTAL NATIONAL FEE =					$1000.00	
Fee for recording the enclosed assignment (37 CFR 1.21 (h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property. +					$40.00	
TOTAL FEES ENCLOSED =					$1040.00	
					Amount to be refunded:	$
					charged:	$

a. ☒ A check in the amount of $ 1040.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.
A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING**: Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P
1300 I Street, N.W.
Washington, D.C. 20005-3315

DATED: March 2, 2001

SIGNATURE
D. Patrick O'Reilley, Reg. No. 27,932
NAME/REGISTRATION NO.

PREPARING METHOD OF CHIRAL ESTER

BACKGROUND OF THE INVENTION

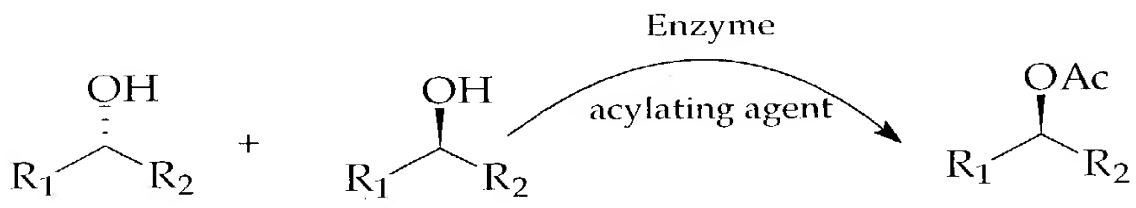
Field of the Invention

The present invention relates to a method for preparing a chiral ester and more particularly, the method for preparing an optically pure chiral ester from a racemic alcohol at a high yield.

Recently, studies for using a metal or an enzyme as a catalyst have been increased in asymmetric syntheses. It has been widely known to use an enzyme as a catalyst for kinetic resolution of a racemic mixture in organic syntheses. A variety of effective methods for hydrolysis of an ester and acylation of an alcohol in the presence of lipase as a catalyst has been reported.

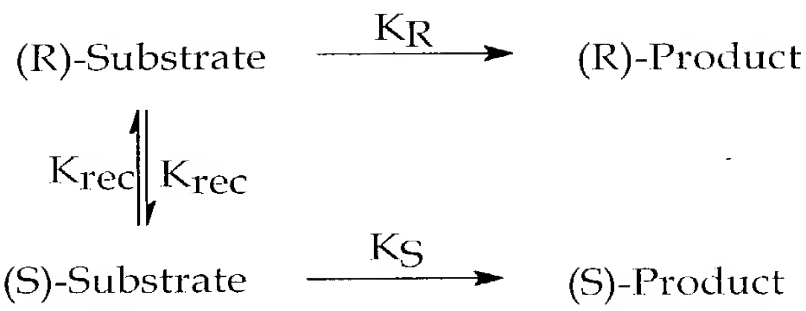
Kinetic resolution is the fact that the two enantiomers react at different rates with a chiral addend. An effective kinetic resolution is the enantioselective conversion from a racemic mixture to an optically pure product as shown in scheme 1, leaving the other enantiomer in a reaction medium.

Scheme 1

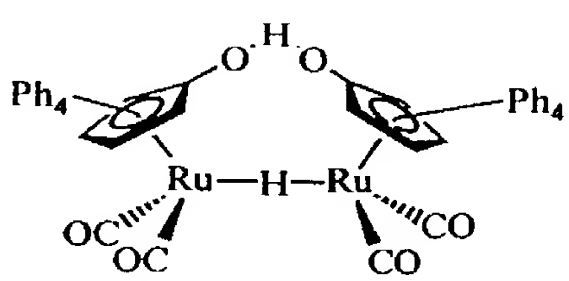


It is well known to prepare a chiral ester from a racemic alcohol by kinetic resolution using esterase. It is possible to obtain an optically pure ester but a maximum yield of this reaction is limited to 50% as shown in scheme 1. Therefore, dynamic kinetic resolution performing kinetic resolution and racemization of an alcohol simultaneously is introduced to resolve such problems (scheme 2).

Scheme 2



The well-known example of a dynamic kinetic resolution is the reaction by using ruthenium complex expressed in the following structure and lipase (Novozym 435) [B. A. Persson, A. L. E. Larsson, M. L. Ray, and J. E. Backvall, *J. Am. Chem. Soc.* 1999, **121**, 1645].



Because racemization of a starting material is performed simultaneously with kinetic resolution, the effectiveness of the starting material is very high and thus, yield of obtaining (R) or (S) enantiomer is theoretically 100%. However, even if the optical purity of a chiral ester obtained by dynamic kinetic resolution is 99 e. e.%, 12 to 40% of ketone as a by-product is produced.

SUMMERY OF THE INVENTION

Therefore, an object of the present invention is to provide a process for preparing an optically pure chiral ester from a racemic alcohol by dynamic kinetic resolution with minimum production of a ketone.

Detailed Description of the Invention

A process for preparing a chiral ester of the present invention is

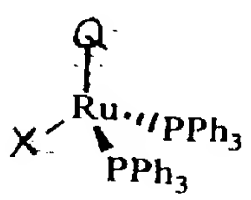
characterized by reacting:

a racemic alcohol;

a ruthenium complex selected from the group consisting of compounds 1, 2 and 3 expressed in formulas 1 to 3 to activate racemization of said racemic alcohol;

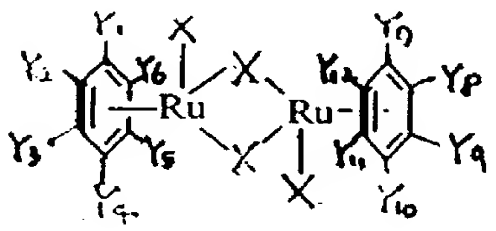
a lipase to acylate selectively one of enantiomers of said racemic alcohol; and

an acyl donor group to supply acyl group to said lipase,



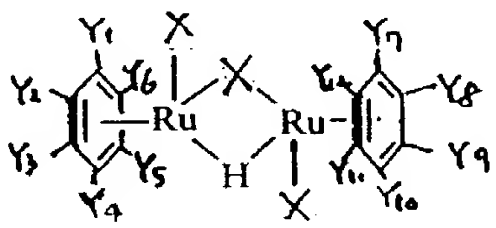
(1)

wherein Q is  or  ; and X is Br, Cl or I;



(2)

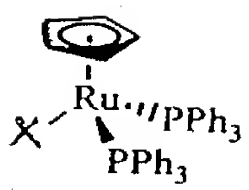
wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I.

Said ruthenium complex is selected from the group consisting of the compounds 5 to 12 expressed in the following formulas 5 to 12,



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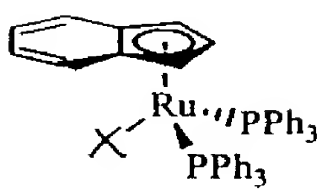

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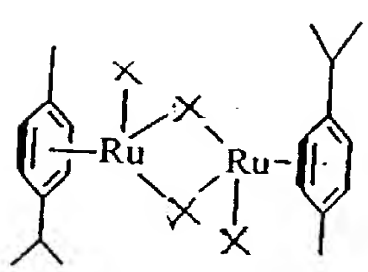

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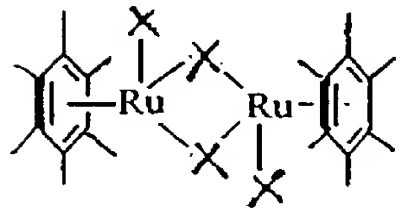

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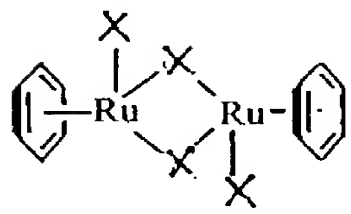

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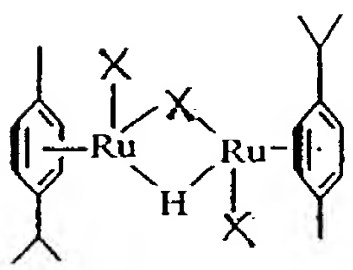

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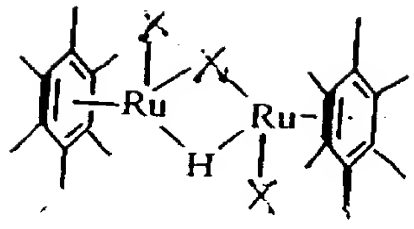

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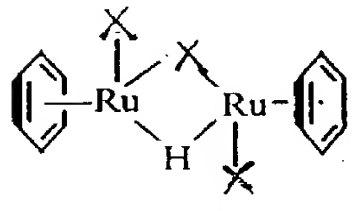


(12)

wherein X is Cl, Br or I, the most preferably Cl.

Preferred content of ruthenium complex is 0.1 to 5 mol%, relative to a racemic alcohol. If the content is more than 5 mol%, cost becomes expensive. On the other hand, if it is less than 0.1 mol%, the rate of the reaction becomes too slow.

A method for preparing a chiral ester from a racemic alcohol by dynamic kinetic resolution is described in detail as set forth hereunder.

A mixture of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is reacted in a solvent in the presence of a base shown in Scheme 3,

Scheme 3

(4) (100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such

as a halogen atom and a cyano group.

A reaction condition varies with a structure of ruthenium complex. When the ruthenium complex of formula 6 is used, an oxygen gas is required essentially in the reaction and it is performed at a temperature of 40 to 60℃. Said oxygen gas reacts with phosphine, which is a ligand bonded with ruthenium, to convert to phosphine oxide. When the ruthenium complex of formula 7 is used, the reaction is performed at a temperature of 20 to 40℃. When the ruthenium complex of formula 10 is used, the reaction is performed at a temperature of 20 to 40℃. A base is also required to remove acid generated during the reaction. Said base includes triethylamine or diisopropylethyl amine but it is not limited to these examples.

The ruthenium complex of formula 7 is commercially available and is converted to the ruthenium complex of formula 10 in alcohol/base condition. Therefore, results from the ruthenium complex of formula 7 and the ruthenium complex of formula 10 are almost same.

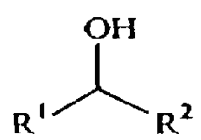
A mechanism of a reaction of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is described in detail hereunder.

An acyl group supplied from the acyl donor compound is reacted with lipase and this lipase is further reacted with one enantiomer of a racemic alcohol selectively to produce a chiral ester. The other enantiomer is racemized by reacting with ruthenium complex. And further one enantiomer from this racemic alcohol is acylated selectively by lipase and this reaction is repeated to produce optically pure chiral ester with preventing generation of ketone which is a by-product in conventional dynamic kinetic resolution.

Reaction solvent is not limited but it is preferred to use methylene chloride, toluene, benzene, or hexane because a solvent commonly affects

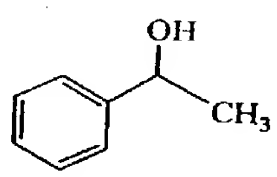
production yield in enzymatic catalysis reaction. An amount of said solvent is used to be 0.2 to 0.3 M concentration of a racemic alcohol.

Said racemic alcohol is generally expressed in the formula 4. It is not limited but examples of the present invention are the following compounds 4a, 4b, 4c, 4d, 4e or 4f,

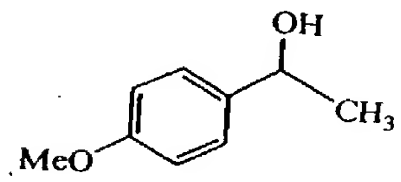


(4)

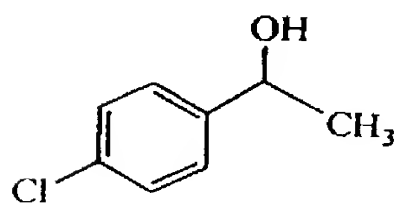
wherein R^1 and R^2 are the same as defined above.



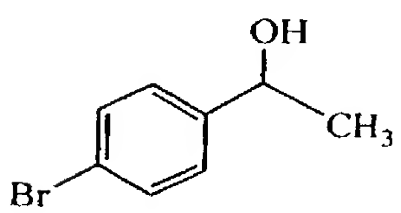
(4a)



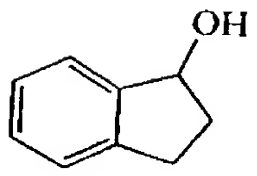
(4b)



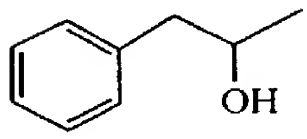
(4c)



(4d)



(4e)



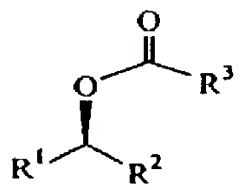
(4f)

Said lipase, which is esterase, acylates one enantiomer from a racemic alcohol selectively to a chiral ester. Examples of lipase are *Pseudomonas cepacias* lipase and *Candida antarctica* lipase and more particulary, *Candida antarctica* component B lipase supported on acrylic resin (Novozym 435, Novo company) or *Pseudomonas cepacias* lipase supported on ceramic particle (lipase PS-C, Amano company). An amount of said lipase is in the range of 10 to 60mg, preferably 30 mg, relative to 1 mmol of an alcohol in Novozym 435 case, and is in the range of 50 to 320 mg, preferably 160 mg, relative to 1 mmol of an alcohol in lipase PS-C case.

Said acyl donor supplies an acyl group to a lipase and acts to move a reaction balance to an acylated product in the presence of a lipase. Preferred acyl donor is aryl ester or alkenyl acetate, the most preferably aryl ester such as *p*-chlorophenyl acetate having electron withdrawing group. An example of alkenyl acetate is isoprophenyl acetate. Such acyl donor compounds are preferred to use because they have an appropriate reactivity without inhibiting racemization. A preferred amount of said acyl donor compound is 2 to 4 equivalents to 1 equivalent of racemic alcohol. If the amount is more than 4 equivalents to 1 equivalent of racemic alcohol, it is difficult to isolate after a reaction. On the other hand, if it is less than 2 equivalents to 1 equivalent of racemic alcohol, the rate of acylation becomes too slow.

A chiral ester expressed in formula 100 is obtained by reacting a racemic

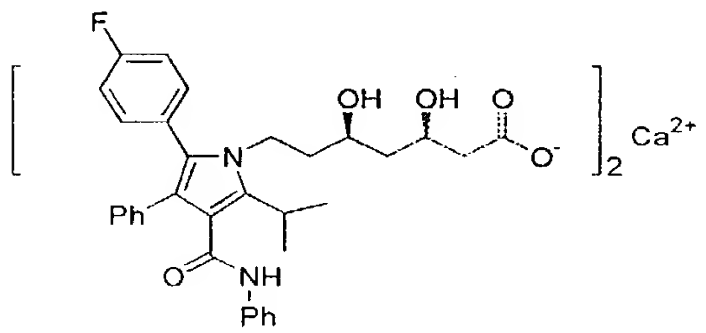
alcohol, a ruthenium complex, a lipase, and an acyl donor compound,



(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

The chiral ester of formula 100 of the present invention can be used as a synthetic intermediate for preparing various chiral compounds, chiral pharmaceutical drugs or chiral agrochemicals and more particularly, used as an essential intermediate for preparing Atorvastatin expressed in formula 101 which is a useful drug for treatment for hyperlipemia, L-Carnitine expressed in formula 102 which is as an additive used in food and drugs, and Agenerase expressed in formula 103 which is an essential intermediate of AIDS drug.



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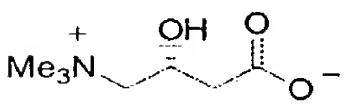

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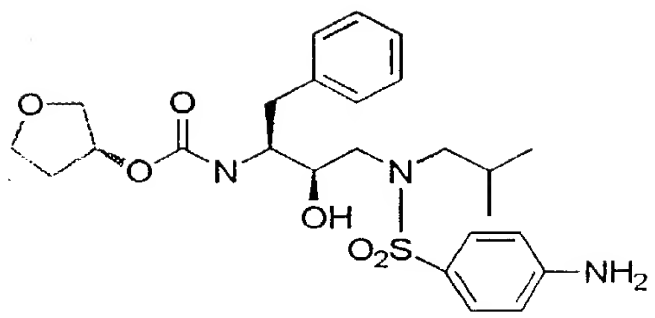
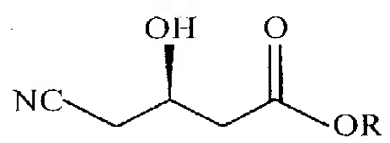


(103)

Especially, a chiral compound of formula 100a which is one of the compounds of the present invention is a key intermediate for preparing Atorvastatin of formula 101 disclosed in US Patent No. 5,908,953,



(100a)

wherein R is a low alkyl group.

The process for preparing a chiral ester of formula 100 of the present invention provides minimum production of by-products such as unreacted alcohol residue up to less than 10% and maximum production of product up to 98% having a high optical purity of 99% or more. Because optical purity is the most important factor in preparing chiral compounds for food and pharmaceutical drugs, the chiral ester of the present invention can be used as a useful starting material in various fields, especially fine chemical field.

The following examples are intended to be illustrative of the present invention and should not be construed as limiting the scope of this invention defined by the appended claims.

Example 1

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.75mmol), ruthenium complex of formula 6(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 2.0ml of dichloromethane to give a redish brown suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition. Oxygen(0.0130mmol) was injected with syringe in the reaction suspension and then it was heated at 60℃ for 43 hours.

Examples 2-6

The product, a chiral ester, was prepared by the same procedure of Example 1 except to use racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 7

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 7(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

Examples 8-12

The product, chiral ester, was prepared by the same procedure of Example 6 except to use racemic alcohols of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 13

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 10(0.0100mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene

chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

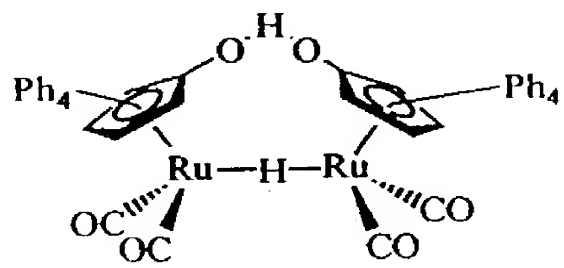
Examples 14-18

The product, chiral ester, was prepared by the same procedure of Example 11 except to use a racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Comparative Example 1

A racemic alcohol of formula 4a(2mmol), ruthenium complex expressed in the following structure below(0.04mmol), 60mg of Novozym 435, and *p*-chlorophenyl acetate(6mmol) were mixed in 5ml of toluene to give a dark redish suspension.

The reaction suspension was heated at 70℃ for 46 hours under argon gas.



Comparative Examples 2-5

The product, a chiral ester, was prepared by the same procedure of Comparative Example 1 except to use racemic alcohols of formulas 4b, 4d, and 4e and octan-2-ol instead of a racemic alcohol of formula 4a.

Yield, optical purity, and formation of ketone of each reaction of

Examples 1-15 and Comparative Examples 1-5 were determined and tabled in Table 1. Said yield was analyzed by ^{1}H-NMR spectrum, and said optical purity was determined by high performance liquid chromatography. Said ^{1}H-NMR spectrum was taken by using Bruker AM 300 and said high performance liquid chromatography was SpectraSystem P2000.

Table 1

Section	Formation of ketone (%)	Yield (%)	Optical purity (e.e.%)
Example 1	0	85	96
Example 2	0	82	99
Example 3	0	98	99
Example 4	0	91	95
Example 5	0	85	97
Example 6	0	92	96
Example 7	8	90	94
Example 8	10	90	99
Example 9	8	90	99
Example 10	8	92	99
Example 11	8	83	99
Example 12	7	91	98
Example 13	5	95	94
Example 14	7	93	99
Example 15	5	93	97
Example 16	4	96	99
Example 17	4	85	99
Example 18	4	95	99
Comp. Example 1	20	Below 80	-
Comp. Example 2	40	Below 60	-

Comp. Example 3	22	Below 78	-
Comp. Example 4	23	Below 77	-
Comp. Example 5	20	Below 80	-

As shown in Table 1, the amount of a ketone formed as a by-product in Comparative Examples 1 to 5 is in the range of 20 to 40% while that in Examples 1 to 18 is less than 10%. Therefore, the yield of the final product, a chiral ester, prepared by Examples 1 to 18 is much more improved.

As a result, it is proved that the present invention provides a process for preparing an optically pure chiral ester from a racemic alcohol with minimizing the formation of ketone at a high yield in the presence of catalysts which are ruthenium complex selected from formulas 1, 2, and 3, and lipase.

CLAIMS

What is claimed is :

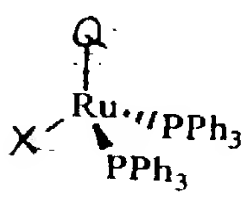
1. A process for preparing a chiral ester expressed in formula 100 by reacting;

a racemic alcohol of formula 4;

a ruthenium complex selected from the group consisting of compounds 1, 2, and 3 expressed in formulas 1, 2, and 3 to activate racemization of said racemic alcohol;

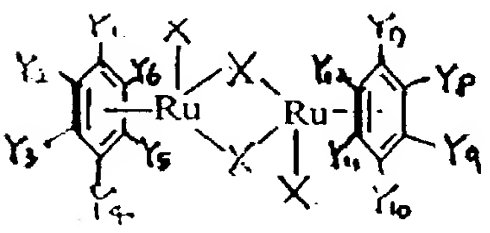
a lipase to acylate one enantiomer selectively from said racemic alcohol; and

an acyl donor compound to supply acyl group to said lipase,



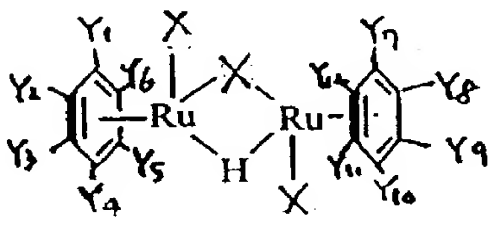
(1)

wherein Q is  or  ; and X is Br, Cl or I;



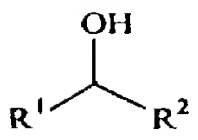
(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; and



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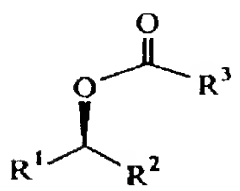
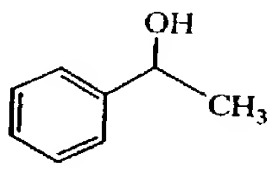


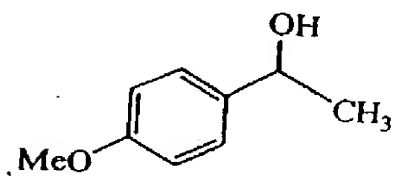
(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

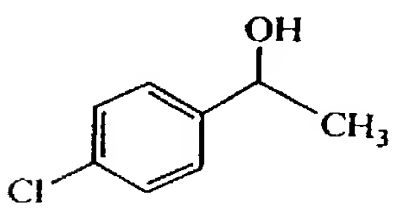
2. The process for preparing a chiral ester according to claim 1, wherein said racemic alcohol is selected from the group consisting of the compounds 4a, 4b, 4c, 4d, 4e and 4f.



(4a)



(4b)



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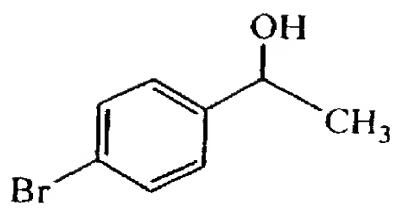

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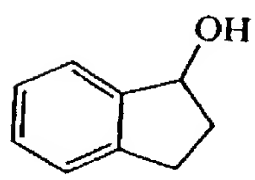

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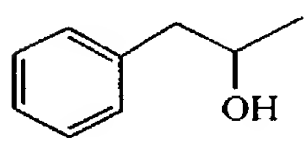
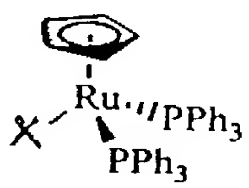


(4f)

3. The process for preparing a chiral ester according to claim 1, wherein said lipase is selected from the group consisting of *Pseudomonas cepacias* lipase and *Candida antarctica* lipase.

4. The process for preparing a chiral ester according to claim 1, wherein said ruthenium complex is selected from the group consisting of compounds 5, 6, 7, 8, 9, 10, 11 and 12,



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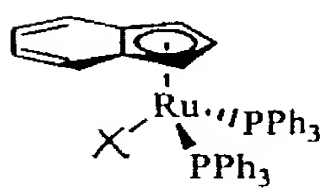

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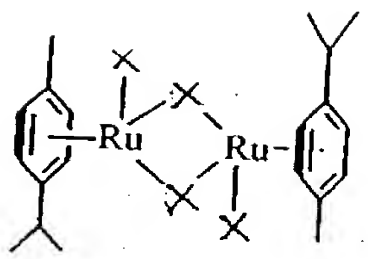

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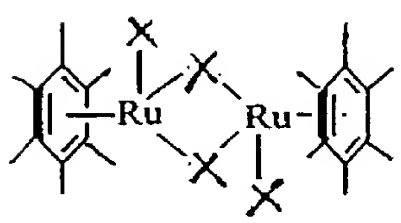

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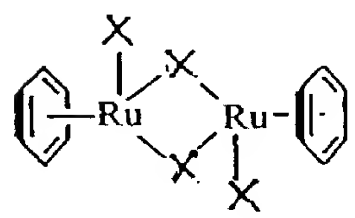

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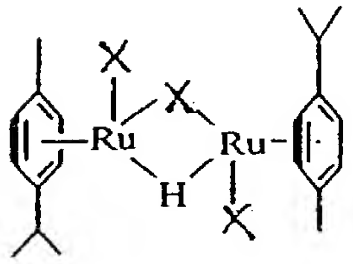

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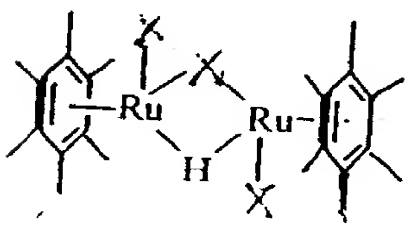
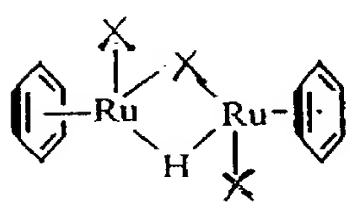


(11)



(12)

wherein X is Cl, Br or I, the most preferably Cl.

5. The process for preparing a chiral ester according to claim 3, wherein X is Cl.

6. The process for preparing a chiral ester according to claim 1, wherein said reaction requires use of oxygen gas.

7. The process for preparing a chiral ester according to claim 1, wherein a content of said ruthenium complex or its derivatives is in the range of 0.1 to 5mol% to said racemic alcohol.

8. The process for preparing a chiral ester according to claim 1, wherein said acyl donor compound is aryl ester.

9. The process for preparing a chiral ester according to claim 7, wherein said aryl ester is selected from the group consisting of *p*-chlorophenyl acetate and alkenyl acetate.

ABSTRACT

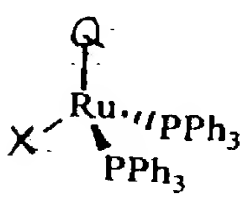
The present invention is to provide a process for preparing a chiral ester expressed in formula 100 by reacting;

a racemic alcohol of formula 4;

a ruthenium complex selected from the group consisting of compounds 1, 2, and 3 expressed in formulas 1, 2, and 3 to activate racemization of said racemic alcohol;

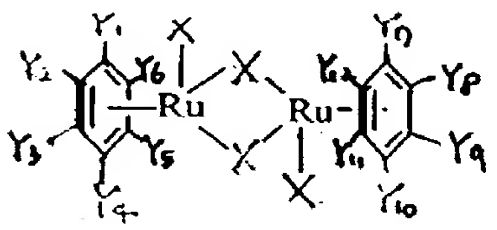
a lipase to acylate one enantiomer selectively from said racemic alcohol; and

an acyl donor compound to supply acyl group to said lipase,



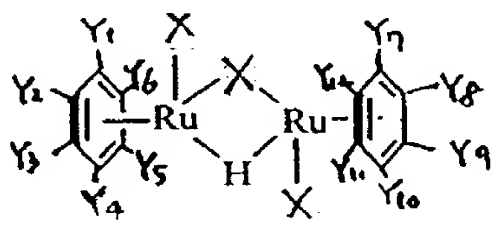
(1)

wherein Q is  or  ; and X is Br, Cl or I;



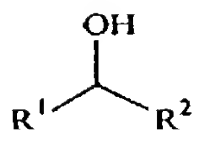
(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; and



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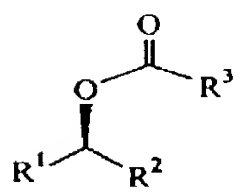

(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

Attorney Docket No.: _____

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PREPARING METHOD OF CHIRAL ESTER

the specification of which:

is attached hereto; or

was filed as United States Application Serial No. _____
on _____, and was amended on _____
(if applicable) or

was filed as PCT International Application Number PCT/KR00/01170
on October 18, 2000, and was amended on _____
(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT International application(s) designating at least one country other than the United States, listed below and have also identified below, any foreign application(s) for patent or inventor's certificate, or any PCT International application(s) having a filing date before that of the application(s) of which priority is claimed:

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119	
Korea	99-45040	October 18, 1999	x YES	□ NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Date of Filing

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior Unites States or PCT International application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International filing date of this application:

Attorney Docket No.: ____________________

Application Number	Date of Filing	Status (Patented, Pending, Abandoned)

I hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.**, Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,487; David W. Hill, Reg. No., 28,220; Thomas L. Irving, Reg. No. 28, 619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Habeman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No.32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg.
62. No.32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Dirk D. Thomas, Reg. No. 32,600; Thomas W. Banks, Reg. No.32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmonson, Reg. No. 33,871; Michael R. McGurk, Reg. No.32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; and Linda A. Wadler, Reg. No. 33,218; and ____.
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Attorney Docket No.: _____

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Full Name of Fourth Inventor	Inventor's Signature	Date
4-00 JUNG, Hyun Min	Jung. H. M	Nov. 9. 2000
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Post Office Address Same as above		